classification has been demonstrated, the situation comes under the second paragraph of MPEP 803 which requires search and examination of both groups.

Claim 1 reads as follows:

> A method of treating a tumor in a subject, which comprises administering to said subject an effective amount of at least one agent that decreases the $[GSH]^2/[GSSG]$ ratio in the malignant cells of said tumor, wherein said at least one agent is administered continuously to said patient for a period of time within the range of from about 15 to about 75 hours.

Claim 5 reads as follows:

> A method of treating a tumor in a subject, which comprises administering to said subject an effective amount of a synergistic combination of at least two agents that decrease the $[GSH]^2/[GSSG]$ ratio in the malignant cells of said tumor, wherein said agents are selected from the classes consisting of:
> (i) an agent that oxidizes GSH, or a precursor thereof;
> (ii) an agent that forms an adduct or a conjugate with GSH, or a precursor thereof;
> (iii) an agent that inhibits the GCS enzyme; and
> (iv) an agent that inhibits the glutathione reductase (GR) enzyme,

As pointed out previously and above, applicants submit that there should be no restriction requirement.

Claim 1 defines administering <u>at least one agent</u> and this definition includes <u>at least two agents</u> recited in claim 5. In addition, both claims 1 and 5 recite "...administering to said subject <u>an effective amount</u> of ... at least ... agent that decrease the $[GSH]^2/[GSSG]$ ratio..."; and the term "effective amount" is defined in page 12, lines 9-19, as "...the amount administered to

maintain continuously the *E* of the cancer cell at about -190 to -200 mV for a time, *tau*, which retards the proliferation … When a combination of agents is used, the combined amount that is pharmaceutically active is a quantity of the two or more agents which, when combined and administered to maintain continuously the *E* of the cancer cell at about -190 to -200 mV for a time, *tau*, which retards the proliferation…"

Thus, the methods of Groups I and II achieve the same objective, i.e., treatment of a tumor by decreasing the $[GSH]^2/[GSSG]$ ratio in malignant cells, by the same method steps and not by employing different method steps, as stated in the Office Action. Therefore, the methods of Groups I and II are, in effect, a sole invention, and the restriction requirement should be withdrawn.

Withdrawal of the restriction requirement is in order and is respectfully requested.

The election of species requirement is somewhat different then the requirement for election of species made in the earlier Office Action, namely in the designation of the patentably distinct species of Group II. In the first election of species requirement, applicants had to elect one compound from each of the species (i) to (iv) in claim 5. Thus, in the Reply filed on November 4, 2005, to the first Office Action, invention II was elected together with the species disulfiram for agent (i), curcumin for agent (ii), buthionine sulfoximine (BSO) for

agent (iii), and carmustine for agent (iv). Now applicants are required to elect not a single compound but a combination of two agents acting in synergistic fashion as defined in claim 5. For Group II, the following 5 species are found:

SPECIES 1: synergistic combination of (i) and (ii);
SPECIES 2: synergistic combination of (i) and (iii);
SPECIES 3: synergistic combination of (i) and (iv);
SPECIES 4: synergistic combination of (ii) and (iii);
SPECIES 5: synergistic combination of (ii) and (iv).

With regard to the election of the species, the Office Action designates Species 1-5, each reciting a combination of two agents only.

However, claim 5 defines "...combination of at least two agents...selected from ... (i)...(ii)...(iii)...and (iv)..."; and, based on Example 4, applicants wish to elect (with traverse and without prejudice) a Species 6 consisting of a synergistic combination of three agents as defined in claim 5 (i), (iii) and (iv), and more specifically: disulfiram for agent (i) (claims 6-7 and 9-13), buthionine sulfoximine (BSO) for agent (iii) (claims 10-11 and 14), and carmustine for agent (iv) (claims 12-13 and 15).

As applicants' presently preferred embodiments involve the presence of all three agents (i), (iii) and (iv), applicants submit that they have a right to elect such embodiments

comprising these agents, even though this is not set out as a possibility in the Office Action.[1] Claims 1 and 5 are generic.

Applicants respectfully traverse the requirement for the same reason set forth in the Reply of November 4, 2005, in the second paragraph on page 3, respectfully repeated by reference.

Applicants respectfully await the results of a first examination on the merits.

Respectfully submitted,

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[1] Applicants' species election should be fully acceptable as indicated above. Nevertheless, if for some reason it is not acceptable, and in order to avoid further delay in the prosecution of the present application, applicants would secondarily elect species 2, namely a combination of disulfiram for agent (i) (claims 6-7 and 9-13) and buthionine sulfoximine (BSO) for agent (iii) (claims 10-11 and 14).